IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:

Siegfried ANSORGE et al. Examiner: SIMMONS, CHRIS E

Serial No.: 10/584,072 Group Art Unit: 1612

Filed: April 3, 2007 Confirmation No.: 6887

Title: **USE OF AT LEAST ONE EFFECTOR OF GLUTATHIONE METABOLISM TOGETHER WITH ALPHA-LIPOIC ACID FOR THE TREATMENT OF CHRONICALLY OBSTRUCTIVE LUNG DISEASES**

REPLY BRIEF

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Supplemental Reply Brief is submitted under 37 C.F.R. §41.41 in response to the Examiner's Answer mailed May 13, 2010.

1. Rejections withdrawn:

(None)

2. Rejections maintained:

The rejection of claims 1-3, 5-8 and 10-15 under 35 USC §103(a) as allegedly unpatentable over Biewenga et al. (*ABB*, 1994), Mira et al. (*Biochem. Pharmacol.*, 1994) further in view of Yeadon (US publication No. 2004-0167153; *hereinafter* the '153 publication) has been sustained.

The Examiner continues to contend that Biewenga's disclosure on the usefulness of α-lipoic acid against lung emphysema in combination with Mira's

disclosure of the use of silibinin as an antioxidant and HOCl scavenger, *prima facie* renders obvious the claims of the instant application. The Examiner's main points are outlined in the paragraphs bridging pages 8 and 10 of the Examiner's Answer, wherein it is alleged that:

(a) Insofar as the primary Mira et al. (*Biochem. Pharmacol.*, 1994) and the secondary Biewenga et al. (*ABB*, 1994) respectfully teach that silibilin and lipoic acid are useful for the same purpose (i.e., reduction of HOCl), a skilled artisan would have been motivated to combine the two agents for the treatment of COPD. The Office Action appears to allege that molecules such as α-lipoic acid and silibilin that quench HOCl are *de facto* effective against COPD. However, such is not the case. The references, even at their broadest interpretation, are limited to a disclosure of *in vitro* reduction of HOCl levels via treatment with α-lipoic acid or silibilin individually. Yeadon discloses "combination therapy using aerosol or dry powder formulations for simultaneous, sequential or separate administration by the inhaled route in the treatment of obstructive airways or other inflammatory disease, such as, asthma or emphysema...[and] does not expressly teach lipoic acid or siliblin." Yeadon's combinations are directed to PDE4 inhibitors of Formula I and β receptor agonists (e.g., formoterol or salmeterol) and use thereof for the treatment of obstructive airways. The therapeutic compounds of Yeadon act differently (i.e., indirectly via enzymatic inhibition) than the presently claimed compounds. More importantly, there is no mention of any ROS scavenging molecules or any combination of such in Yeadon. Mira and Biewenga are also silent on this issue. In short, none of the cited references teach or suggest that the claimed combination of α-lipoic acid and silibilin can used in the treatment of COPD. See, independent claim 1. To this end, the Examiner is cordially requested to review the BPAI's decision in *Ex parte Wada and Murphy*, Appeal No. 2007-3733 (decided: January 14, 2008), wherein it was held that a holding of obviousness under §103(a) is unjustified in instances where the Office Action fails to articulate where or how the cited art teaches

or suggests all of the features of a claimed invention. Applicants submit that the asserted combination of cited references fails to teach or suggest each and every feature of independent claims 1 and 5. For example, the asserted combination of references does not teach or suggest treatment of COPD using a combination of silibinin and α-LA. At most, Mira and Biewenga teach *in vitro* reduction of HOCl using the compounds of the instant application.

It should be noted in this context that although the treatment of COPD appears in the preamble of aforementioned claims 1 and 5, patentable weight should be given to this feature in accordance with the Federal Circuit's decision in *Catalina Marketing International v. Coolsavings.com, 62 USPQ2.d 1781* (Fed. Cir. 2002). Therein the Court stated that one instance where the preamble is to be given weight is where it is essential to understand terms used in the claim body (at 61 USPQ2.d 1785). Such is clearly the case here where reference to "dose of a combination" is made in the body of claim 1, which in turn relates to the asserted use of such combinations in "cytoprotective treatment of chronically obstructive lung."

(b) With regard to demonstration of unexpected properties, the Examiner contends that:

(1) The data in Tables 6 and 7 do not show "superadditive" effects. The Examiner performs simple arithmetic tests to allege that the increase in intracellular thiol concentrations and macrophage phagocytosis as a result of treatment with the claimed combination are not significant. This contention is respectfully traversed. At the outset Appellants submit that the disclosure in the specification is presumptively valid and the burden rests on the Examiner to show otherwise. See *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971). Insofar as the specification states that the effects were superadditive, the Examiner's assertion (even if the simple arithmetic analyses provided in the Office Action are held to be correct) is without legal merit. More importantly, it is not understood why the Examiner would refuse to accept the

objective assertions of statistical significance, which are explicitly made in pages 14 and 16 of the present specification. For example, based on a robust analysis of variance (ANOVA) test, it was deduced that the claimed combination significantly ameliorates intracellular thiol concentration compared to treatment with α-liopic acid or silibinin alone (see the values marked with an asterisk * in Table 6). The same is true with regard to the study of the effects of the claimed combination on the rate of macrophage phagocytosis, the results of which are presented in Table 7.

Although not required, purely to aid in the Examiner's understanding, enclosed herewith are the results of *student's t-test* comparing the mean intracellular thiol concentration (ITC) values recited in the aforementioned Example 4 using online version of PRISM® program (available free of charge through GraphPad Software, Inc., La Jolla, CA, USA). Exhibit A shows calculations using the values provided in Table 6. Similarly, the mean phagocytosis levels recited in Table 7 of Example 5 were compared using *student's t-test*, the results of which are presented in Exhibit B. In these analyses, it was hypothesized that intracellular thiol concentration (ITC) for the combination [ITC(combo)] would be expected to be greater than the ITC for the untreated samples [ITC(control)], samples treated with α-lipoic acid alone [ITC(LA)] and samples treated with silibilin alone [ITC(sili)]. It was also hypothesized that the phagocytosis by cells treated with the combination [phagocytosis(Combo)] would be greater than that of the control cells [phagocytosis (control)], cells treated with LA alone and cells treated with silibilin alone. The respective legends of Tables 6 and 7 provide details on the sample size (n) and the parameters that were measured (i.e., means, standard deviations, etc.). Using these numbers, the *p value* for a 1-tailed student's t-test (i.e., statistically significant difference) was calculated for all samples analyzed.

As demonstrated in Exhibit A, treatment of COPD cells with the asserted

combination of α-liopic acid and silibinin was found to statistically improve intracellular thiol levels compared to treatment with α-liopic acid or silibinin alone (*p-value* <<0.05). Similarly, for the results in shown in Table 7 (N = 6), the asserted combination of α-liopic acid and silibinin was found to statistically improve phagocytosis compared to α-liopic acid or silibinin alone (*p-value* <0.05 for 1-tailed test). See enclosed results from GraphPad Prism.

(2) The Examiner further proceeds to contend that even if the claimed combination conferred super-additive effects, the data are not commensurate with the scope of the claimed subject matter (i.e., synergism is not evident at all concentrations for silibilin). To this end, the Examiner at page 10 alleges that 10 μg/ml of lipoic acid + 700 μg/ml of silibilin showed a lower ITC compared to control. Firstly, the presence of inoperative embodiments within the scope of the claim does not challenge the validity of the claim. Inoperative embodiments are permissible within a claim. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. See, e.g., *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984) and MPEP §2164.08(b), which is in accord. A skilled worker understands that the effects of any effector molecule (i.e., drug) are saturated at some dose/concentration. At even higher concentrations, the effects may also turn to be undesirable (e.g., due to toxic effects, etc.). The Examiner's pointing out that the combination with the highest dosage of silibilin (700 μg/ml) reduces ITC does not undermine the objective assertions made in the instant specification regarding the super-additive effects of the claimed combination. A skilled worker has all the guidance as to the dosages at which the individual agents confer the desired pharmacological effects and the dosages at which the effects are super-additive. Explicit recitation of the dosages is not necessary at all. To this end, Applicants note that dependent

claims 2, 3, 13, 14 and 15 recite dosages of the individual components. The specification provides explicit guidance on the dosages of each agent at which the therapeutic effect of the asserted combination is super-additive.

(3) The Examiner continues to allege that "proper showing of unexpected results would include a comparison to 80 μg of lipoic acid alone and 80 μg of silibinin alone." This contention is without merit because there is no requirement that the exact same doses of α-lipoic acid and silibilin be used in the comparative assessment. All is required is that the amounts of the respective agents in the combination be identical to that which is used in singularity. Such has been established by the present disclosure.

For the above reasons and the reasons set forth in Appellants' Brief, it is submitted that the decision of the Examiner finally rejecting claims 1-3, 5-8 and 10-15, on appeal, is in error and should be reversed.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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EXHIBIT A

(Intracellular Thiol Concentration)

Unpaired *t* test results

P value and statistical significance:
The two-tailed P value equals 0.0007
By conventional criteria, this difference is considered to be extremely statistically significant.

Confidence interval:
The mean of ITC(combo) minus ITC(control) equals 40.900
95% confidence interval of this difference: From 20.781 to 61.019

Intermediate values used in calculations:
t = 4.3600
df = 14
standard error of difference = 9.381

Learn more:

GraphPad's web site includes portions of the manual for GraphPad Prism that can help you learn statistics. First, review the meaning of P values and confidence intervals. Next check whether you chose an appropriate test. Then learn how to interpret results from an unpaired or paired *t* test. These links include GraphPad's popular *analysis checklists*.

Review your data:

Group	ITC(combo)	ITC(control)
Mean	102.500	61.600
SD	22.600	13.900
SEM	7.990	4.914
N	8	8

QuickCalcs Online Calculators for Scientists

1. Select category 2. Choose calculator 3. Enter data **4. View results**

Unpaired *t* test results

P value and statistical significance:
The two-tailed P value equals 0.0017
By conventional criteria, this difference is considered to be very statistically significant.

Confidence interval:
The mean of ITC(combo) minus ITC(LA) equals 42.200
95% confidence interval of this difference: From 18.806 to 65.594

Intermediate values used in calculations:
t = 3.8690
df = 14
standard error of difference = 10.907

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Review your data:

Group	ITC(combo)	ITC(LA)
Mean	102.500	60.300
SD	22.600	21.000
SEM	7.990	7.425
N	8	8

QuickCalcs Online Calculators for Scientists

1. Select category 2. Choose calculator 3. Enter data **4. View results**

Unpaired *t* test results

P value and statistical significance:
The two-tailed P value equals 0.0002
By conventional criteria, this difference is considered to be extremely statistically significant.

Confidence interval:
The mean of ITC(combo) minus ITC(Sili) equals 46.400
95% confidence interval of this difference: From 26.852 to 65.948

Intermediate values used in calculations:
t = 5.0911
df = 14
standard error of difference = 9.114

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Review your data:

Group	ITC(combo)	ITC(Sili)
Mean	102.500	56.100
SD	22.600	12.400
SEM	7.990	4.384
N	8	8

EXHIBIT B

(Phagocytosis assay)

Unpaired *t* test results

P value and statistical significance:
The two-tailed P value equals 0.0782
By conventional criteria, this difference is considered to be not quite statistically significant.

Confidence interval:
The mean of Phagocytosis(Combo) minus Phagocytosis(Control) equals 18.600
95% confidence interval of this difference: From -2.529 to 39.729

Intermediate values used in calculations:
t = 1.9614
df = 10
standard error of difference = 9.483

Learn more:

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Review your data:

Group	Phagocytosis(Combo)	Phagocytosis(Control)
Mean	75.500	56.900
SD	17.300	15.500
SEM	7.063	6.328
N	6	6

Unpaired *t* test results

P value and statistical significance:
The two-tailed P value equals 0.0817
By conventional criteria, this difference is considered to be not quite statistically significant.

Confidence interval:
The mean of Phagocytosis(Combo) minus Phagocytosis(LA) equals 16.500
95% confidence interval of this difference: From -2.498 to 35.498

Intermediate values used in calculations:
t = 1.9352
df = 10
standard error of difference = 8.526

Learn more:

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Review your data:

Group	Phagocytosis(Combo)	Phagocytosis(LA)
Mean	75.500	59.000
SD	17.300	11.700
SEM	7.063	4.777
N	6	6

Unpaired *t* test results

P value and statistical significance:
The two-tailed P value equals 0.0404
By conventional criteria, this difference is considered to be statistically significant.

Confidence interval:
The mean of Phagocytosis(Combo) minus Phagocytosis(Sili) equals 20.400
95% confidence interval of this difference: From 1.091 to 39.709

Intermediate values used in calculations:
t = 2.3541
df = 10
standard error of difference = 8.666

Learn more:

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Review your data:

Group	Phagocytosis(Combo)	Phagocytosis(Sili)
Mean	75.500	55.100
SD	17.300	12.300
SEM	7.063	5.021
N	6	6